PATENT
Attorney Docket No. **CASE-03330**

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Richard P. Woychik *et al.*
Serial No.: 09/103,846 Group No.: 1632
Filed: 06/24/98 Examiner: Jill D. Martin
Entitled: **ALLELIC SERIES OF GENOMIC MODIFICATIONS IN CELLS**

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

CERTIFICATE OF MAILING UNDER 37 CFR § 1.8(a)

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to the: Assistant Commissioner for Patents, Washington, D.C. 20231, on **April 18, 2000**.

By: Marlene Garitano
Marlene Garitano

Sir:

Applicants have become aware of the citations listed below, copies attached, which may be material to the examination of the above-identified application, and which are therefore submitted in compliance with the duty of disclosure defined in 37 C.F.R. §§ 1.56 and 1.97. The below-listed items were cited by the International Search Report in a counterpart PCT application. The Examiner is requested to make the following citations of official record in this application.

Also enclosed is a check for the fee set forth in 37 CFR §1.17(p) in accordance with 37 CFR §1.97(c)(2) for filing an Information Disclosure Statement after the mailing date of a first Office action on the merits and before the mailing date of either a final action or a notice of allowance.

- Kanbashi *et al.* (1997) "Frameshifts, base substitutions and minute deletions constitute X-ray-induced mutations in the endogenous *tonB* gene of *Escherichia coli* K12," Mutation Research 385:259-267. Kanbashi *et al.* discloses X-ray irradiation of *E. coli* cells to induce mutations in the endogenous *tonB* gene.

Mutant cells were selected for resistance to colicin (ColB^r) by culturing irradiated cells in colicin. Only one mutant colony was ultimately derived from each irradiated culture, and the type of mutation in each colony was determined by DNA sequencing. Kanbashi *et al.* also discloses that X-rays induced frameshift, base substitution, deletion, inversion, translocation, and insertion mutations in the *tonB* gene of *E. coli*. However, Kanbashi *et al.* does not disclose using a chemical agent to modify a gene of interest in isolated embryonic cells;

- Woychik *et al.* (1998) "Functional genomics in the post-genome era," Mutation Research 400:3-14. This item is not prior art. As shown in the enclosed dated receipt stamp (Tab 1), Woychik *et al.* appears in a journal which was received on August 26, 1998 by the Health Sciences Library at the University of Wisconsin, Madison. Since the receipt date is more than two months after the filing date (6/24/98) of the instant application, Woychik *et al.* is not prior art;
- Hera *et al.* (1996) "Use of an infectious Simian virus 40-based shuttle vector to analyze UV-induced mutagenesis in monkey cells," Mutation Research 364:235-243. Hera *et al.* discloses the effects of transfecting COS7 monkey cells with the πSVPC7 shuttle virus on the UV-induced mutations in COS7 cells. Hera *et al.* discloses that COS7 which are either untreated or pretreated with UV are infected with virus which is either untreated or UV-irradiated. To determine whether these protocols resulted in mutations in the extrachromosomal *supF* gene in COS7 cells (*i.e.*, SupF$^-$ mutants), plasmid DNA is isolated from infected cells and shuttled into a strain of *E. coli* (MBM7070). While MBM7070 colonies are bright blue, resulting E. coli transformants which contain plasmids with a mutated *supF* gene are isolated as white or light blue colonies on indicator plates containing X-Gal and IPTG. To determine the type of mutation in the *supF* gene, the *supF* gene of mutant E. coli colonies is amplified with PCR and sequenced. Unlike the claimed invention, Hera *et al.* does not disclose using a chemical agent to modify a gene of interest in isolated embryonic cells;

- Guay-Woodford *et al.* (1996) "Evidence that two phenotypically distinct mouse PKD mutations, *bpk* and *jcpk*, are allelic," Kidney International 50:1158-1165. Guay-Woodford *et al.* discloses that the *bpk* mutation in the polycystic kidney disease (PKD) arose spontaneously in the BALB/c inbred mouse strain, while the *jcpk* mutation was induced by chlorambucil mutagenesis of mice. Guay-Woodford *et al.* is distinguished from the claimed invention in that it does not disclose using a chemical agent to modify a gene of interest in isolated embryonic cells. Rather, Guay-Woodford *et al.* uses whole mice as targets for chlorambucil treatment;
- Bultman *et al.* (1991) "Molecular characterization of a region of DNA associated with mutations at the agouti locus in the mouse," Proc. Natl. Acad. Sci. USA 88:8062-8066. Bultman *et al.* discloses molecular characterization of mice containing six mutations at the agouti (*a*)-locus. The mice were generated by treating female mice (containing oocytes) with X-rays or γ rays, or treating male mice (containing spermatogonia) with ethyl methanesulfonate, γ rays or methylnitorsourea. The resulting treated animals were bred to generate progeny mice, whose liver or tail DNA was used for Southern hybridization to determine the type of mutation in the agouti-locus. The mutations induced were as follows: (1) the a^{Jl10} mutation was induced by treating oocytes with X-rays, (2) the a^{Jl41} mutation was induced by treating spermatozoa with ethylmethanesulfonate, (3) the a^{Jl85} mutation was induced by treating oocytes with γ rays, (4) the $a^{9H¶}$ mutation was induced by treating oocytes with X-rays, (5) the Is1Gso mutation was induced by treating spermatogonia with γ rays, and (6) the a^{5MNU} mutation was induced by treating spermatogonia with methylnitorsourea. This disclosure is distinguished from the claimed invention since Bultman *et al.* does not disclose treating isolated embryonic cell, but rather whole mice. Furthermore, Bultman *et al.* does not disclose isolating the treated oocytes and spermatogonia after treatment with a chemical agent;
- Woychik *et al.* (1990) "Molecular and genetic characterization of a radiation-induced structural rearrangement in mouse chromosome 2 causing mutations at the limb deformity and agouti loci," Proc. Natl. Acad. Sci. USA 87:2588-2592.

Woychik *et al.* discloses irradiating male mice of *a* locus genotype A/A^{w} with γ rays, and mating these males with females of different *a* locus genotypes to generate a mutant non-agouti male mouse containing an inversion of chromosome 2. Woychik *et al.* is distinguished from the claimed methods in that it does not disclose treating isolated embryonic cells with a chemical agent. Rather, Woychick *et al.* used irradiation was of whole animals;

- You *et al.* (1997) "Generation of radiation-induced deletion complexes in the mouse genome using embryonic stem cells," Methods: A Comparison to Methods in Enzymology 13:409-421. You *et al.* discloses a strategy to create radiation-induced deletions in mouse ES cells. This strategy involves integration of a negatively selectable marker into a predetermined locus by homologous recombination, treatment of targeted cells with radiation, selection for loss of the marker, and characterization of the deletion sizes in the ES cell by PCR or Southern analysis. Clonal cell lines containing desired deletions are then used for generation of chimeric mice. In contrast to the claimed methods, You *et al.* does not employ a chemical agent, but rather radiation.

This Information Disclosure Statement under 37 C.F.R. §§ 1.56 and 1.97 is not to be construed as a representation that a search has been made, that additional information material to the examination of this application does not exist, or that any one or more of these citations constitutes prior art.

Dated: April 18, 2000

Kamrin T. MacKnight
Registration No. 38,230

MEDLEN & CARROLL, LLP
220 Montgomery Street, Suite 2200
San Francisco, California 94104
(415) 705-8410